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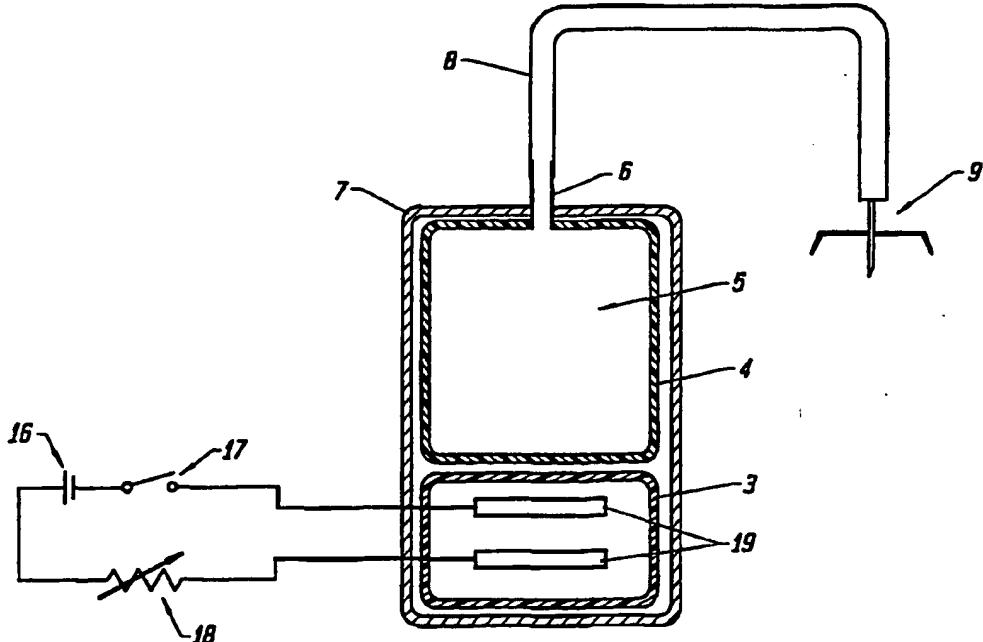
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(54) Title: CONTROLLED RELEASE INFUSION DEVICE



(57) Abstract

A portable infusion device assembly, having two pouches (3, 4) in pressure transmitting relationship, the first (4) containing infusate and the second (3), a driving medium (2). The driving medium (2) is pressurized by activation of osmotic pump, electrochemical reaction, release of pressurized fluid or gas or mechanical means, and the rate of infusion is controlled by a rate controlling means. The infusate pouch is separately manufactured and can be stored apart of the rest of the system.

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## CONTROLLED RELEASE INFUSION DEVICE

### 5 FIELD OF THE INVENTION

This invention relates to controlled release infusion devices, and particularly to small portable body-mounted devices capable of delivering liquids such as drugs or other pharmaceutical agents for prolonged periods, where the liquid is contained in a flexible pouch within the device.

### 10 BACKGROUND OF THE INVENTION

Many kinds of parenteral drug therapy require continuous drug delivery in preference to single or multiple drug injections. Benefits that accrue from continuous therapy may include, for instance, reduction of toxic or other side effects associated with sharp pulses of drug, significant improvement in the effectiveness of the therapy through the use of smaller amounts of drug, and increased patient comfort. The traditional manner of administering sustained parenteral treatments is via intravenous drip. Intravenous drip treatment is commonplace in a hospital environment, but this treatment mode obviously imposes severe restrictions on the activity of the recipient. As a result, considerable research over the last few years has been devoted to the development of small portable infusion pumps. A range of devices has appeared, including those with electric or clockwork motors that drive syringe or peristaltic pumps, and others powered by the elastic tension of an inflated balloon, or the vapor pressure of a volatile propellant. Literature incorporated herein by reference describing such pumps are *Controlled Release Micropump for Insulin Administration*. (M.V. Sefton et al., Ann. Biomed. Eng., Vol. 7, pp. 329-343, 1979), *Continuous Intravenous Arabinosyl Cytosine Infusions Delivered by a New Portable Infusion System*, (J. Bottino et al., Cancer, Vol. 43, pp. 2197-2201, 1979), or product brochures from Auto-Syringe, Inc., Hooksett, New Hampshire and Cormed, Inc., Medina, New York. These devices are typically strapped onto the wearer, or carried on a belt or in a harness. Also, most are designed to deliver relatively large quantities of fluid and do not effectively dispense small volumes of the order of a few milliliters or less.

An alternative approach that has been exploited to a limited extent is to drive the infusion device osmotically, using a Rose-Nelson pump, activated by imbibition of water or other driving fluid. The principle of the osmotic pump was originally conceived by Rose and Nelson in the 1950's (S. Rose and J.F. Nelson, "A Continuous Long-Term Injector," *Austral. J. Exp. Biol.* 33, pp. 415-420 (1955)). A Rose-Nelson pump consists of three chambers: a salt chamber containing excess solid salt, a drug chamber, and a water chamber. The salt and water compartments are separated by a rigid membrane permeable to water but impermeable to ionized and hydrated salt ions; the salt and drug chambers are separated by a rubber diaphragm. In operation, water is imbibed osmotically into the salt chamber, causing the rubber diaphragm to expand into the drug chamber and forcing the drug out through the delivery orifice. Depending on the salt used, the osmotic pressure developed by this type of pump is usually between 50 and 200 atmospheres. The pressure required to pump the drug from the device is small in comparison, and hence the drug delivery rate remains constant as long as some excess undissolved salt remains in the salt chamber. In comparison with mechanically-driven devices, Rose-Nelson pumps are small, reliable, and simple and inexpensive to manufacture. U.S. Patent 3,604,417 discloses a modification of the Rose-Nelson pump in which a movable piston replaces the elastic diaphragm separating the drug and salt chamber, and both the drug and salt are loaded into the pump as solutions. U.S. Patent 4,474,048 discloses another modification of the Rose-Nelson principal employing an impermeable elastic wall, and a movable end wall that can be screwed in to deliver a pulse dose of the contained drug at any time during the operation of the pump. U.S. Patent 4,474,575 is a variant of 4,474,048 in which the flow rate of the dispensed agent can be varied by altering the area of semipermeable membrane exposed to the water chamber. U.S. Patent 4,552,651 discloses a pump assembly with a small osmotic pump that can be filled in advance of use with the active agent to be dispensed. The action of this pump is initiated by filling the lower chamber of the housing with a hydrogel. Once the pump is in action, an optional mechanism for delivering pulse doses can be employed. All these osmotic pumps are self-driven and begin to operate as soon as all of the several chambers are filled with

their fluid contents and liquid is imbibed across the semipermeable membrane into the salt chamber.

U.S. Patent 4,838,862, commonly owned with the present application and incorporated herein by reference in its entirety, describes a portable osmotic infusion pump that can be filled with the agent to be dispensed, the osmotic salt and the driving medium, and then stored as a complete assembly, ready for activation and use without need for addition of other components. U.S. Patent 4,898,582, also commonly owned with the present application and incorporated herein by reference in its entirety, describes a portable osmotic pump that includes a housing with two side-by-side compartments, where one compartment contains the osmotic salt chamber, and the second compartment contains the imbibing liquid for the pump. The latter two patents describe osmotic pumps that can be filled with all required fluids, including the drugs to be delivered, stored until needed, and then activated very rapidly on demand. They are therefore excellent systems for use as disposable drug infusion devices.

Many limitations of these infusion devices, however, have not yet been addressed or resolved. One common limitation of some of these systems is that the patient does not have control over activation of the device, or has, at best, only limited control. For example, if a device is activated by ingestion, it will begin to release drug as soon as it comes into contact with internal fluids. Another limitation is that, for many of these systems, the delivery rate of the infusate is not controlled, and, in particular, cannot be controlled by the user. A related problem is that, for many of these devices, the delivery rate of the infusate is controlled by directly regulating the flow of the infusate out of the device, for example, by a valve to control the flow rate. This configuration presents problems with sterilization of the device, due to the presence of small compartments and crevices in contact with the infusate that may be difficult for the sterilizing agent to reach. Another problem with flow regulation of the infusate fluid is that shear effects created, for example, by fluid passing through a valve, may lead to degradation of the molecules of drug in solution. For example, proteins or other large molecules are particularly susceptible to shear degradation. Moreover,

reliable regulation of these very low flow rates is inherently difficult.

Yet another limitation of some of these devices is that long-term storage of the devices presents problems associated with drug stability and integrity. Many substances such as drugs fare poorly when stored, especially when stored in solution. The drug, when stored  
5 in a delivery device for a period of time, may change or deteriorate chemically and pharmacologically, and may precipitate out of solution. The drug may also react chemically with other components of the system that diffuse from various parts of the assembly into the drug chamber. This aspect of production, sterilization, and storage of a drug-bearing device is not adequately addressed in available disposable infusion devices and is a problem that  
10 therefore limits their use. Another limitation of some of these devices is related to the fact that there is, commonly, only one barrier between the infusate and driving medium, for example, a rubber diaphragm. This configuration creates potential safety problems for the user. Any tear or leak in the wall of the reservoir containing the infusate permits mixing of the infusate with the driving medium, which will result in contamination of the infusate.  
15 Such contamination would be potentially harmful to the patient if it happened during use and went undetected, particularly if the driving fluid were contaminated by bacteria or other harmful substances. Clearly, it is possible to choose a driving medium that would not be harmful to the patient if this accidental mixing were to occur, but the requirement of sterilization of the driving medium, and preservation of the driving medium's sterility during  
20 use, is yet another obstacle in the creation of a device that is simple and cost-effective to manufacture.

One means for resolving the problems of long-term infusate storage that is described in detail in this application is accomplished by containing the infusate in a removable flexible pouch within the device. In one embodiment of the invention, the pouch could be a part of  
25 the device that is filled with the infusate during manufacture, or later, for example by a pharmacist or other person, a short time before the device is used. There are many instances in the patent literature of infusion pumps where the liquid infusate is contained in a separate pouch within the device. U.S. Pat. 4,034,756 discloses a small osmotic pump for use in an

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aqueous environment, such as the gastrointestinal tract, in which the liquid infusate (e.g. a drug solution) is contained in a flexible bag within the device, and the osmotic fluid pressure is exerted directly on the flexible bag to effect infusate delivery. The flexible bag of this patent can be filled with the infusate during pump manufacture, or the bag can be filled with the infusate at a later time. This pump can be activated only by exposure to the aqueous environment, and is therefore limited generally to internal use for drug delivery. The activation means consists of the user swallowing the device or otherwise exposing the device to internal fluids, and rate control is solely a function of the permeability characteristics of the outer semipermeable layer.

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U.S. Patent 3,760,805 describes an osmotic dispenser comprised of a water porous housing confining a first flexible bag of relatively impervious material containing an active agent, and a second bag of controlled permeability to moisture containing an osmotic solution. The first and second bags are disposed within the housing such that water permeates from the external environment through the housing and migrates by osmosis into the solution contained in the second bag. The second bag increases in volume, thereby generating mechanical force on the first bag, which mechanical force in turn ejects the active agent out of the device. This pump, designed primarily for ingestion or implantation, depends upon permeation of water from the environment, e.g. gastrointestinal tract, and therefore is unsuitable for subcutaneous infusion.

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U.S. Pat. 4,201,207 discloses an elastic bladder pump filled with liquid under pressure, which is powered by the elastic tension of the bladder. The bladder can be filled with infusate liquid during or after manufacture. This device also includes a flow control element between the bladder and the catheter fitting to deliver the liquid infusate to the patient.

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Because the flow control element operates on the liquid infusate to be delivered, it has some of the attendant problems with shear effects and sterilization as described above. In addition, the bladder must be made of elastic materials, which are inherently permeable. The infusate is therefore vulnerable to absorption of contaminants by diffusion into the infusate from and through the bladder as well as loss of the drug by diffusion through the bladder if it is stored

in the bladder for extended periods of time.

U.S. Pat. 4,191,181 discloses a liquid infusion pump with a power supply such as a battery and a refillable flexible infusate reservoir. This pump can be activated on demand and has a flow control means that acts directly on the pumping mechanism, which is downstream from the infusate reservoir. Therefore, the rate control means, in this case the pump mechanism, comes in direct contact with the infusate, causing the attendant problems with sterilization and shear effects described above.

U.S. Pat. 4,596,575 discloses an implantable liquid infusion pump that is particularly intended for the delivery of insulin. It contains two collapsible reservoirs in rigid housings, and also a mechanical pump that is regulated by an electronic unit control for management of pump activation and flow rate. One of the reservoirs contains the infusate; the space between the outer wall of this reservoir and its rigid housing is filled with the drive liquid. The second reservoir is filled with the drive liquid, and the space between the outer wall of this reservoir and its rigid housing is maintained at subambient pressure. The drive liquid is pumped from the second reservoir into the outer space of the first housing to exert pressure on the first reservoir and thus deliver the liquid infusate. The electronic control unit regulates two valves that restrict the flow rate of the drive liquid; thus the infusate does not come in contact with the valving system. The device is also provided with a separate refill system that may be used to refill the infusate reservoir. This type of refill mechanism, however, presents sterility problems during long-term use, particularly because it is used in an implantable device that cannot be cleaned during use. In addition, if the pouch wall breaks or tears, the infusate is susceptible to contamination from the driving medium, as described above.

Other patents in the literature describe portable infusion pumps that contain flexible pouches containing the infusate fluid that are removable from the device, or that can be loaded separately into the device after manufacture of the main pump assembly. U.S. Pat. 4,193,398, for example, discloses an extracorporeal osmotic pump in which the infusate liquid is contained in a flexible pouch that is located within a second pouch containing the osmotic

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fluid. In one embodiment, the infusate pouch can be removed from the main pump assembly and be replaced. This pump also contains an additional chamber filled with the driving medium for the pump, for example water or a weak osmotic solution, and incorporates rate-control and activation means. The osmotic fluid, however, has the potential to be in direct contact with the outer wall of the infusate pouch. Therefore, diffusion of the osmotic fluid into the infusate, and resulting damage, can occur if the infusate is stored within its pouch for any length of time in its fully assembled state. In addition, if the pouch wall breaks or tears, the infusate is susceptible to contamination from the osmotic fluid, as described above.

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U.S. Pat. 4,398,908 discloses an infusion pump driven by electromechanical power, in which insulin is stored in a flexible pouch that is removable and replaceable, as is the pumping mechanism described. This pump can be activated on demand and incorporates a rate-control mechanism. The pumping mechanism, which incorporates the activation and rate-control means, is downstream from the insulin reservoir, and therefore comes in direct contact with the insulin infusate. As a result, this design has problems with sterilization of the pumping mechanism during manufacture, and shear effects on insulin during use, as described above. Insulin, being a large biomolecule in solution, is particularly susceptible to such damage.

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U.S. Pat. 4,525,164 discloses a motor-driven pump with a removable and replaceable arcuated reservoir, in which a piston applies pressure directly to a portion of the reservoir to propel the drug out of the device. This device incorporates a means for activating the pump motor and controlling the pumping rate. Because the piston acts directly on the outer wall of the infusate reservoir, however, there is the possibility of shear effects on the infusate drug. Also, maintaining sterility in the pouch and pumping mechanism is difficult.

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Each of these references describes an infusion pump that incorporates a separately loaded pouch or reservoir in a specific configuration, and usually with a specific motive force, yet all have problems that have inhibited their use. These problems include a high cost of manufacture, difficulties in sterilizing the drug chamber and contents, difficulties in maintaining sterility of the device, and problems with stability of the devices after

prolonged storage. As a result, there remains a need for a reliable disposable infusion pump that can be loaded with sterile liquid infusate, that can maintain sterility during prolonged storage, and that can be activated on demand to provide the required pattern of delivery of very low infusate flow rates.

5       The present invention describes an infusion pump assembly that incorporates an infusate pouch that can be manufactured, sterilized, and aseptically loaded with infusate and assembled into a sterile pump assembly or sterilized separately from the other components of the assembly and then loaded into the pump assembly at the appropriate time. The pump is small, light, and convenient for patient use, and may be driven by a variety of motive  
10      forces in its different embodiments. The infusate pouch of this invention is simple in design, and therefore would be straightforward to manufacture and sterilize. It can also be made of nonelastic materials and therefore can be constructed using materials that are relatively impervious to invasion by environmental agents such as oxygen, carbon dioxide, or substances that are derived from components of the device. The rate of delivery of the infusate from  
15      this pouch is controlled by the expansion of a second pressure-transmitting pouch. Pressure is obtained by filling the second pressure-transmitting pouch with a driving medium at a controlled rate.

20      Presentation of sterile medication to the patient via infusion devices presents several unique problems in drug stability and sterility. Deposition of a drug solution into a cavity within an infusion device just prior to application requires presterilization of that cavity and delivery of a unit dose of sterile drug to the aforesaid cavity in an aseptic manner. Some methods of sterilization may be suited for some materials but totally unacceptable for other desired components. Many drugs and solutions may be rendered sterile by gamma radiation, but polypropylene components subjected to sterilizing doses of gamma radiation suffer severe  
25      radiation induced degradation. Metals may be advantageously sterilized using steam, but many drugs cannot withstand the steam sterilization regime. Separation filling and sterilization of the infusate pouch from the manufacture and treatment of the remainder of the infusion device permits optimization of the sterilizing procedure. For example, the

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infusate pouch may be manufactured and sterilized under conditions most suited for the materials of pouch construction. Then, at a later date, the sterile pouches may be aseptically filled with unit doses of drug solution that have been presterilized by conventional means; or alternately, the solutions may be sterilized by sterile filtration at the point of filling and the pouches sealed. These sterile dose units may then be assembled into the remainder of the infusion device or stored and shipped separately. Since the contents of the infusate pouch do not come into direct contact with the other components of the pump, it is not essential that the remainder of the device be manufactured and maintained under sterile conditions.

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Drugs that have limited lifetimes in solution may be stored in a dry or lyophilized form in a two-component embodiment of the infusate pouch. In this pouch, one compartment contains the drug and another contains solvent for the drug in a separate sealed part of the pouch. The seal between the two compartments is broken just prior to use, the contents are mixed in the pouch, the pouch loaded into the infusion device, and the device is activated and attached. In this way, the shelf-life of the drug is dependent solely upon the storage

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conditions of the drug-containing infusate pouch.

#### SUMMARY OF THE INVENTION

##### Objects of the invention.

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It is an object of the invention to provide a portable controlled release infusion device that can be stored, with or without the infusate, for prolonged periods without deterioration.

It is an object of the invention to provide a disposable portable controlled release infusion device that can be stored, with or without the infusate, for prolonged periods without deterioration.

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It is another object of the invention to provide a portable controlled release infusion device wherein each individual device could potentially be used to deliver any of a variety of different liquids, including different drugs.

It is another object of the invention to provide a portable controlled release infusion device wherein the infusate is protected from contamination by other substances, particularly

fluids, in the device, both during storage and use of the device.

It is another object of the invention to provide a portable controlled release infusion device that is inexpensive and straightforward to manufacture.

5 It is another object of the invention to provide a portable controlled release infusion device that can be easily sterilized and maintained in a sterile state.

It is another object of the invention to provide a portable controlled release infusion device that can be activated quickly and simply on demand.

10 It is another object of the invention to provide a portable controlled release infusion device wherein the flow rate of delivery of the liquid infusate can be controlled, either by the design of the device, or preferentially chosen by the user.

Other objects and advantages of the invention will be apparent to those of ordinary skill in the art from the description that follows.

Brief description of the drawings.

**FIGURE 1** is a diagram of the basic features of the invention.

15 **FIGURE 2** is a diagram of an embodiment of the invention for which the motive force is electrolysis of a fluid to produce a gas that will act as the driving medium.

**FIGURE 3** is a diagram of an embodiment of the invention for which the motive force is an expanding gas that exerts pressure on the driving medium.

20 **FIGURE 4** is a diagram of an embodiment of the invention for which the motive force is the elastic tension of a driving medium under pressure in an elastic compartment.

**FIGURE 5** is a diagram of an embodiment of the invention in which a mechanical or electromechanical motive force drives the device.

25 **FIGURE 6** is a diagram of an embodiment of the invention for which the infusate is contained in lyophilized form in a pouch with two compartments, with a seal separating the infusate from a liquid solvent.

Description of the invention. To achieve the foregoing objects, the present invention provides a portable controlled release infusion pump assembly. The assembly includes two chambers, where two containers (an elastic pouch and a flexible pouch) are held in the first

chamber and a power source is contained in the second chamber. The first chamber is contained in a restraining outer housing that restricts movement of the two pouches. Preferably, the entire device is contained in a second unitary protective housing so as to protect the device from the environment. The protective housing can be made of metal or plastic, and would normally be made by any conventional mass-production technique. The dimensions of the housing will vary according to the volume of the chambers that are contained. The first chamber of the pump houses a first flexible pouch that is preferably sterilizable and under neutral pressure. This flexible pouch contains the infusate, preferably in liquid form. This first chamber also houses a second pouch, called the pressure-transmitting pouch, containing the driving medium as it is pumped in or created by the pressure-generating means. These pouches are positioned in the chamber with a minimal free volume between the pouches, and the pouches have a shared surface area by which pressure is transmitted from the pressure-transmitting pouch to the pouch containing the infusate. Preferably, these two pouches completely fill the chamber in which they are placed. The assembly also includes a second chamber that contains the power source as herein defined, which consists of a pressure-generating means, an activating means, and a means of controlling the pressure increase or the rate of generation or transfer of the driving medium into the pressure-transmitting pouch, and thus the infusate flow rate out of the device. In a preferred embodiment, the pressure-generating means is based on the principle of osmosis as in the Rose-Nelson pump, described above. In other embodiments, the pressure-generating means is based on other motive principles, such as electrolysis, gas expansion, or elastic pressure. In all cases, the pressure-generating means will cause the delivery of a fluid, the driving medium, to the pressure-transmitting pouch, which will then exert pressure on the infusate delivery pouch. This driving medium can be a liquid or gas, and activation of the device by the user will cause delivery of the driving medium to the pressure-transmitting pouch. The rate at which the driving medium enters the pressure-transmitting pouch will be controlled by the rate-controlling means, which may be a membrane, in the case of a pump based on the Rose-Nelson principle, or in other embodiments of the device may be a

valve for controlling fluid flow, or in still other embodiments of the device, may be a means of controlling current or voltage of an electric circuit. The resulting delivery rate of the infusate to the needle assembly is thus dependant on the pressure created in the pressure-transmitting pouch. The invention described herein is intended to deliver low flow rates, up to several milliliters per day, of infusate solution to the patient, and thus is primarily intended for subcutaneous, as opposed to intravenous, delivery. The infusion apparatus as herein described may be used for intravenous therapy where the flow rates of infusate are compatible with the intended intravenous therapy.

In the embodiment described above, the first chamber contains a pouch that contains the infusate. Because the infusate pouch can be manufactured and filled separately from the rest of the device, it can be sterilized in a manner optimal for the drug and the pouch material. Thus, drugs that are sensitive to radiation, steam, or ethylene oxide sterilization can be filled into presterilized pouches by sterilizing filtration under aseptic conditions. The remainder of the pump components may be sterilized under more rigorous conditions or not sterilized at all. In one embodiment, the infusate pouch and its contents are stored separately from the rest of the pump assembly under conditions particularly suited for the drug, thus greatly increasing the shelf life of the completely assembled pump. Because only the infusate pouch material, the needle assembly, and the delivery tube come in contact with the infusate solution, only these components need be sterile.

The infusate pouch is constructed of flexible material that is relatively impermeable to both the infusate contained (on its inner surface) and, as insurance against leakage of the pressure-transmitting pouch, the driving medium (on its outer surface), during storage and use. The material used for manufacture of this pouch should be flexible so that pressure applied by the pressure-transmitting pouch to the infusate pouch causes delivery of the infusate. It is important that the materials used to fabricate the infusate pouch lack any substantial resistance to transmission of pressure developed in the pressure-transmitting pouch. That is, pressure developed in the pressure-transmitting pouch should be almost exactly transmitted to the infusate pouch, which will lead to flow of infusate out of the

infusate pouch. Elastic materials can be used but are not preferred because most elastic materials are poor barriers to diffusion and could, in some cases, result in loss of the drug or permit interaction with chemicals diffusing into the infusate pouch of the driving medium, if this fluid should leak out of the pressure-transmitting pouch. In addition, elastic materials are typically more vulnerable to attack and degradation caused by infusate solutions.

5 Therefore, preferred materials for the infusate pouch are polyethylenes, polypropylenes, Teflon® (E.I. Du Pont de Nemours & Co., Wilmington, DE), Barex® (BP Chemicals International, Cleveland, OH), Tedlar® (Du Pont), and polyfoil laminates of materials such as polyethylene (facing the drug solution) and aluminum foil outside the pouch.

10 The infusate contained in the infusate pouch may be in its final fluid form ready for delivery. In some instances, however, it may be preferable to store the infusate, e.g. a drug, in a lyophilized or otherwise desiccated form, in order to prolong the storage time of the drug. This would be of particular interest if the infusate pouch were to be stored with the rest of the pump assembly during the entire shelf life of the device. Therefore, in an alternate embodiment, the infusate pouch will be segmented into two compartments. One compartment will contain a lyophilized form of the infusate, and the other compartment will contain a liquid solvent. In this embodiment, a seal between the two compartments would be broken by the user, or by a pharmacist or the like, before or during activation of the pump for use. To protect the infusate from degradation by diffusion of foreign substances into the drug-containing portion of the pouch during storage, and in particular the solvent, the seal must be made of impermeable materials. Preferred materials include metallized foil, metallized plastic film, and the like. This embodiment allows for storage of the infusate for long periods of time while insuring that the sterility of the pouch environment is not violated.

15 In an alternate embodiment, the infusate pouch will contain a lyophilized form of the infusate, and the user or pharmacist will add a liquid solvent in an aseptic manner to the pouch either before or during activation of the pump.

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As previously discussed, the pressure-transmitting pouch is in pressure transmitting relationship with the infusate delivery pouch and contains the driving medium as it is

pumped into the pressure-transmitting pouch or generated by the power source. The pressure-transmitting pouch, and in particular the area that is in pressure transmitting relationship with the infusate delivery pouch, is made of flexible and preferably elastic materials so that it can exert pressure on the infusate pouch as driving medium fills the  
5 pressure-transmitting pouch. These materials of construction should have an extended life and should be impermeable to the driving medium received from the power source so that diffusion through the elastic walls will not contaminate the infusate during the lifetime of the device. Preferred elastic materials include conventional rubbers, ethylene-propylene, butadiene-styrene, neoprene, and the like. The pressure-transmitting pouch contains the  
10 driving medium as it is delivered by or created by the pressure-generating means. In the preferred embodiment of the Rose-Nelson osmotic pump, the driving medium is water. In this preferred embodiment, the pressure-transmitting pouch also contains the osmotic medium prior to activation of the device. Preferred osmotic mediums are salts, salt solutions, such as sodium chloride solution, and organic liquids such as polyethylene glycol. In other  
15 non-Rose-Nelson embodiments of the invention, preferred choices of driving medium are stable liquids such as glycerol, silicone oil, mineral oil, and the like, and gasses such as hydrogen gas. The use of an expanding pouch to transmit pressure to the infusate pouch has a number of advantages over the prior art. First, the driving medium is separated from the infusate by two impermeable films, i.e. the walls of the pressure-transmitting pouch and the  
20 walls of the infusate pouch. This means that even if one film should have a failure that would allow leakage of a confined material, the driving medium will not contaminate the infusate solution, although the pump may continue to deliver fluid out of the infusate pouch. Only in the very unlikely event of leaks or defects being found in both films would contamination occur. This is a considerable advantage over other designs in application for  
25 this type of device, where patient safety is a critical issue. A second problem avoided by this design is the need to make the housing for the infusate pouch and the pressure-transmitting pouch fluid-tight. It should be noted that devices that do not have a separate pressure-transmitting pouch containing the driving medium, for example the system described in U.S.

Pat. 4,596,575, must be made absolutely leak-tight in order to function effectively. This type of construction is difficult to execute in an inexpensive, mass-produced unit, and leakage of the infusate or the driving medium in this type of device on prolonged storage is a serious problem. By containing the driving medium in a pouch, this problem is avoided. In the device described in this invention, it is desirable, however, to have relatively few air pockets in the spaces in the housing outside the pressure-transmitting pouch and the infusate pouch, or in the pressure-transmitting pouch itself. Although it is essential that the infusate pouch and the pressure-transmitting pouch are restrained in pressure transmitting relationship, which can most commonly be obtained by enclosing the pouches in a common housing, one of ordinary skill in the art can design alternative arrangements where the pouches are contained in separate housings and are attached in such a manner to achieve substantially the same results. The various components of this invention, power source, infusate pouch, pressure-transmitting pouch, activating means, rate-controlling means, may all be located within the same housing or in separate housing as convenience dictates, but are intended to be included within the scope of this invention provided that these components have the interrelationships as described herein.

The power source is the third major component of the pump assembly. As previously described, the power source consists of a pressure-generating means, an activation means, and a rate-controlling means. The pressure-generating means causes the delivery of the driving medium (gas or liquid) to the pressure-transmitting pouch. In the Rose-Nelson pump, the pressure-generating means would be the expansion of volume caused by permeation of a fluid through a semipermeable membrane into a salt chamber. Other pressure-generating means include, but are not limited to, electrolysis of a solution to produce a gas as a driving medium, expansion of a gas to generate pressure on a driving medium, storage of a fluid under pressure in an elastic compartment, and mechanical power sources, such as a spring or clock mechanism.

The activation means initiates the delivery of the driving medium to the pressure-transmitting pouch. Thus, the activation means allows for energizing of the pump at the

user's discretion. For a Rose-Nelson pump design, the preferred activation means is rupturing of a seal that separates the permeant from the osmagent. Rupturing of the seal starts the osmotic process that makes it possible for the driving medium to enter the pressure-transmitting pouch. Another possible embodiment of the activation means is an on-off valve  
5 that allows the driving medium to enter the pressure-transmitting pouch. Another possible embodiment is a switch that closes an electrical circuit, or that activates a mechanical source of power.

The rate-controlling means controls the flow of driving medium into, or the creation of driving medium in, the pressure-transmitting pouch. It is a particular advantage of the  
10 present invention that the fluid that is directly controlled is not the infusate, due to attendant problems with maintaining sterility of the rate-controlling means, and the need to avoid shear effects on the infusate. For a Rose-Nelson pump design, the rate-controlling means can be the semipermeable membrane. When the pump is in use, the permeant travels through the semipermeable membrane, and the rate of pumping of fluid to the pressure-transmitting  
15 pouch is thus controlled by the permeation properties of this membrane such as thickness, exposed area, permeation constant, etc. Because it is difficult to control the low flow rates with traditional valving (up to several milliliters per day), it is of particular advantage in this system that the rate-controlling means is inherent in the design. In another possible embodiment, rate-controlling means may be obtained by controlling an electrical resistance  
20 that varies the current or voltage in an electrical circuit. Another possible embodiment may make use of a mechanically controlled flow control valve.

The infusate leaves the infusate pouch through a dispensing nozzle and a connecting means. In one embodiment, the end of the connecting means may be adapted for use with a skin-piercing needle or a standard commercial subcutaneous drug delivery set, for example,  
25 the Sub-Q-Set® (Travenol Laboratories, Deerfield, IL). Alternately the tube may be inserted into one of the normal body orifices.

The device assembly can be attached to the body of the wearer by means of a biocompatible adhesive coating on the base of the assembly, or by adhesive strips or overlays,

and does not mandate the use of straps, belts, or other carrying garments. The device may be attached anywhere on the body that is convenient, either immediately adjacent to the delivery site, or at a point distant from that site.

Particularly when describing the power source of this invention, embodiments will 5 employ components that are dependant on the motive force of the pump, driving medium used, the infusate being delivered, and other variables. The choice of components used in the various foregoing general descriptions and the following detailed descriptions are exemplary and explanatory, but are not restrictive of the invention.

Because the devices described in the present invention are small and simple, they 10 are particularly suitable for delivering small infusate volumes. The pump assembly of this invention, while it can be tailored for a range of infusate volumes and dosage rates, is particularly useful where the total infusate volume to be dispensed is of the order of a few milliliters, and the delivery time for that volume is one to seven days. Thus, the invention enables therapy involving highly potent substances, such as peptide drugs of various kinds, 15 heparin and insulin, analgesics and anesthetics, corticosteroids, immunosuppressants, antineoplastics, antibacterials, and antidotes to chemical or biological poisons and the like, to be administered without subjecting the patient to repeated injections or requiring the patient to be attached to an intravenous drip.

The infusion device can be assembled with its components and stored for periods of 20 months or years without deterioration. In a particularly preferred embodiment, the infusate is stored in the infusate pouch separately from the rest of the pump assembly. When ready for use, the patient or pharmacist or the like can insert the infusate pouch into the device. The device can be activated on demand by the user or therapist.

#### DETAILED DESCRIPTION OF THE INVENTION

25 Definition of terms. The term "drug" as used herein denotes any medication composition (as defined, below); in any way affecting any human or animal entity; substance to be assimilated by any human being or animal for its nourishment or for regulating its growth; substance exhibiting any of the above activities to be directly applied to the habitat,

surroundings or environment of any of the above organisms; and substance having any other effect on any other environment, especially any aqueous environment.

Therefore, suitable drugs for use with the dispenser of this invention include, without limitation, those that are generally capable of:

5        1. Preventing, alleviating, treating, or curing abnormal or pathological conditions of the living body by such means as destroying a parasitic organism or limiting the effect of the disease or abnormality by chemically altering the physiology of the host or parasite;

10      2. Maintaining, increasing, decreasing, limiting or destroying a physiologic body function, e.g. vitamin compositions, sex sterilants, fertility inhibitors, fertility promoters, growth promoters, and the like;

15      3. Diagnosing a physiological condition or state;

15      4. Controlling or protecting an environment or living body by attracting, disabling, inhibiting, killing, modifying, repelling, or retarding an animal or microorganism, such as food and nonfood baits, attractants and lures, biocides, pesticides, algicides, parasiticides, rodenticides, insecticides, fungicides, and the like;

20      5. Preserving, disinfecting, or sterilizing; and

20      6. Controlling or affecting generically an environment, as by introducing a catalyst or metering a reactant into a reacting chemical system, or by effecting any chemical process therein, such as fermentation, including propagation and/or attenuation of a microorganism.

25      Infusate is herein defined as a liquid drug or a solution, gel or suspension of drug that is delivered from the infusate pouch. Driving medium is herein defined as the material contained in the pressure-transmitting pouch that is used to increase the size of the pressure-transmitting pouch. If a gas is generated by the pressure generating means, the driving medium will consist, predominately of a gas. If pressure is generated osmotically, the driving medium will consist of the solution that results when the permeate passes through the semipermeable membrane and contacts the salt or salt solution (osmagent).

Detailed description of the figures. Referring now to the drawings, not drawn to scale, a general plan of the invention is shown in Figure 1. The power source 1 includes a

pressure-generating means, an activation means, and a rate-controlling means. The pressure-generating means in this general plan can be chosen from a variety of motive sources, such as the osmotic pump of the Rose-Nelson type, electrolysis of a liquid to produce a gas as a driving medium, and others as described but not limited to the examples in the figures below.

5       The pressure-generating means causes delivery of the driving medium 2 to the pressure-transmitting pouch 3. As driving medium enters the pressure-transmitting pouch the pouch expands; therefore, the pressure-generating pouch must be made of a flexible or elastic material, and in particular the surface of the pressure-transmitting pouch facing the infusate pouch 4 which contains the infusate 5. Elastic materials are especially preferred because the  
10      surface of the pressure-transmitting pouch 3 that is in pressure transmitting relationship with the infusate pouch functions best when it is expandable. Preferred elastic materials include conventional rubbers, ethylene-propylene, butadiene-styrene, neoprene, and the like. The pressure-transmitting pouch 3 may be made of a single material or can be made by gluing or heat sealing two or more dissimilar materials together to form the pouch.

15      The infusate pouch 4 is made of flexible materials, but normally is not made of elastic materials because most elastic materials are vulnerable to diffusion of the infusate out of the infusate pouch, or of diffusion of the driving medium into the infusate pouch, if this fluid should leak out of the pressure-transmitting pouch 3. In addition, elastic materials would typically be more vulnerable to attack and degradation caused by the infusate  
20      solution. Therefore, preferred materials for the infusate pouch 4 are inert polymers such as polyethylenes, polypropylenes, Teflon® (E.I. Du Pont de Nemours & Co., Wilmington, DE), Barex® (BP Chemicals International, Cleveland, OH), Tedlar® (Du Pont), and polyfoil laminates of materials such as polyethylene (facing the infusate solution) and aluminum foil outside the infusate pouch. It is a major advantage of this invention that the infusate  
25      solution contacts inert, stable, sterilizable, nonleaching materials, and is essentially impervious to contaminants from the outside environment. In one embodiment, the infusate pouch 4 is formed and filled with infusate solution in a single operation using a heat-sealing form-fill-and-seal technology widely used in industry today. This technology is used, for example,

to form small polyfoil bags containing foods such as ketchup and mustard or transdermal drug delivery systems. This technology is amenable to very high production rates at low cost and can be maintained under aseptic conditions.

The pressure-transmitting pouch 3 and infusate pouch 4 are contained in a housing 5 which is restraining and should be made of a substance that is nonirritating to the skin and nonreactive and impervious to the salts, solutions, agents and the like, contained therein. In one embodiment, this housing also encloses the power source, so as to protect it from the environment. In another embodiment, only the pressure-transmitting pouch and infusate pouch are contained in the housing. Preferred materials for housing 7 are stainless steel, 10 aluminum, polyolefins, polycarbonate and the like. An infusate connecting means 8 is attached to the dispensing nozzle 6 of the infusate pouch and by means of the needle assembly 9 to the patient. The needle assembly may be a skin-piercing needle or a standard commercial subcutaneous delivery set, for example, the Sub-Q-Set® (Travenol Laboratories, Deerfield, IL.). Alternately the infusate delivery tube may be inserted into one of the normal 15 body orifices.

Figures 3, 4, 5, 6, and 7 are illustrations of embodiments of the general plan illustrated in Figure 1.

Figure 2 is an illustration of another embodiment of the invention in which the motive force for the pump is provided by electrolysis of a solution to produce gas as a 20 driving medium. The device is activated by a switch 17 that completes an electric circuit consisting of a battery or other power source 16 and a resistance 18. Rate control of the device is achieved either by variation of the voltage or current at the power source 16. A set of electrodes 19 is connected to the electric circuit and is contained in the pressure-transmitting pouch 3. Preferred materials for these electrodes include nickel, palladium, 25 platinum, or other inert materials. The application of current to the electrodes 19 which are immersed in a solution such as sodium sulfate, causes the formation of gas bubbles, for example, bubbles of hydrogen gas. Pressure caused by formation of the gas bubbles is exerted on the area in pressure transmitting relationship between the pressure-transmitting

pouch 3 and the infusate pouch 4 and infusate is delivered to the patient as described in Figure 1. Because large volumes of gasses can be quickly generated by small currents, this type of device is preferred when relatively rapid delivery of the infusate solution is required over a period of a few hours to one day. A second advantage of this unit is that the rate of gas generation, and hence infusate delivery, can be easily changed by varying the voltage or current in the electric circuit. This device therefore allows pulses of infusate to be delivered to the user on demand. This type of system would find an application, for example, in insulin therapy for treatment of diabetes, or analgesic therapy for pain relief.

Figure 3 is an illustration of another embodiment of the invention in which the motive force for the pump is provided by the expansion of a gas under pressure. The gas under pressure 20 is stored in a compartment of the pressure-generating compartment 21 that is separated from the adjoining compartment by an elastic diaphragm 22. This elastic diaphragm must be impermeable so as to prevent migration of the gas into the driving medium during storage, or migration of the driving medium into the gas. Therefore, preferred materials for the impermeable elastic diaphragm include latex rubber, polyisoprene, butyl rubber, nitrile rubber, copolymers of styrene/butadiene, and the like. This gas may be stored as a liquid propellant that vaporizes upon contact with the body; a problem with such a motive means, however, is that the gas pressure will vary with the body temperature, and in particular that a low body temperature would be insufficient to cause sufficient vaporization of the propellant. Therefore, a propellant should be chosen that will vaporize below body temperature at 1 atm, for example, hydrochlorofluorocarbons, or fluorocarbons such as the Freon® refrigerants (E.I. du Pont de Nemours & Co., Wilmington, DE); especially preferred are the Freon refrigerants such as Freon 114 and Freon 21, which vaporize at 3.77°C and 8.92°C, respectively, at 1 atm. Pump action begins after activation means 17 is turned on; this activation means is typically an on-off valve such as a gate valve. When activation means 17 is turned on, the driving medium 2 in the second compartment of the pressure-generating compartment is allowed to flow into pressure-transmitting pouch 3. Preferred choices of driving medium 2 are stable liquids such as water, glycerol, silicone oil,

mineral oil, and the like. The flow rate of the driving medium 2, and therefore the flow rate of infusate from the device, is controlled by manipulation of rate-controlling means 18, which is some type of valve suitable for controlling liquid flow rates in the range, for example, of 0.01 to 5 mL/day. One embodiment of rate-controlling means 18 is an elastomeric micrometering system, consisting of axially-aligned elastic fibers contained in an elastic tube, with a clamping means to adjust the cross-sectional free area in the tube available for fluid flow, as described in *An Elastomeric Micrometering System for the Controlled Administration of Drugs* (J.C. Wright et al., Rubber Chemistry and Technology, Vol. 50, No. 5, pp. 959-968, 1977). As the driving medium enters the pressure-transmitting pouch 3, this pouch exerts pressure on infusate pouch 4 through the area in pressure transmitting relationship between pouch 3 and pouch 4, and infusate is delivered to the patient as described in Figure 1.

Figure 4 illustrates an embodiment of the invention in which the motive force is the elastic tension of a bladder containing a driving medium under pressure in an elastic compartment. The driving medium 2 is contained in elastic compartment 23 under pressure; preferred choices of driving medium 2 are as in Figure 3. Preferred materials for the elastic compartment include conventional rubbers, ethylene-propylene, butadiene-styrene, neoprene, and the like. As in the embodiment of the invention described in Figure 3, the device is turned on using activation means 17, and flow rate of the driving medium, and therefore the infusate, is controlled by rate-controlling means 18. The driving medium is delivered to pressure-transmitting pouch 3, and pressure on infusate pouch 4 results in delivery of the infusate to the patient, as described in Figure 1.

Figure 5 illustrates an embodiment of the invention in which a mechanical motive force 24 drives the pump, i.e. a mechanical pressure generating means creates a force that acts on piston 25 which subsequently exerts pressure on driving medium compartment 26 and forces driving medium 2 out of the compartment. Preferred choices for driving medium 2 are stable liquids such as water, glycerol, silicone oil, mineral oil, and the like. A preferred choice for this mechanical motive source is a battery-powered motor with so-called

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"Accutron" movement made by the Bulova Watch Company (Flushing, N.Y.). A movement of this kind is relatively light in weight and can be obtained designed to turn one revolution per day, so as to drive a drive wheel and piston at one revolution per day. At this speed output a piston can be made to produce approximately 0.42 ounce/inch of torque and with a very nominal increase in speed at this loading. In this system, the rate-controlling means 18 could simply be a means of controlling motor speed, since the rate of delivery of the driving medium is controlled by the motor speed. Another preferred choice for a mechanical pressure generating means is a mechanical spring assembly constructed with a plurality of constant-force extendable coil springs. The extended ends of the spring coils are secured to the piston, which acts upon driving medium compartment 26 upon activation of the device. Thus the spring coils apply a low intensity, constant force to driving medium compartment 26 for developing a small positive pressure on the driving medium 2 contained within the compartment. The device is turned on with activation means 17, which in one embodiment is a solenoid switch, and the flow of driving medium is regulated with rate-controlling means 18, which in one embodiment is a controlled motor speed, as described above. In another embodiment, rate-controlling means 18 is a valve intended for regulating low flow rates as described in Figure 3. The driving medium 2 is pumped into pressure-transmitting pouch 3, and the force applied to the infusate pouch 4 causes the infusate 5 to be delivered to the patient, as described in Figure 1. This type of mechanical driving force is preferred for relatively constant delivery infusion systems.

In another embodiment of the invention, shown in Figure 6, infusate pouch 31 is divided into two compartments for the purpose of storing the drug 27 in lyophilized or otherwise desiccated form, so as to prolong the shelf life of the device. In this embodiment, compartment 30 of infusate pouch 31 contains lyophilized drug and is separated from the solvent compartment 32 of pouch 31 by rupturable seal 29. This seal 29 must be impermeable to both the lyophilized drug 27 and the liquid solvent 28; therefore, a preferred material for this seal is a metallized foil, metallized plastic film, or the like. Seal 29 is ruptured by the user immediately before or during activation of the device, to allow mixing

of lyophilized drug 27 and liquid solvent 28 before delivery of the infusate to the patient.

The invention has been described and illustrated with reference to certain preferred embodiments thereof, but those skilled in the art will appreciate that various modifications, changes, omissions, and substitutions can be made without departing from the spirit of the invention. For example, one skilled in the art might construct the infusion pouch with a fill port so that it may be filled by the user, pharmacist, or the like, just prior to activation. It is intended, therefore, that the invention be limited only by the scope of the following claims. The invention herein described is intended to deliver low flow rates of infusate solution to the patient. For example, such a device might be sized to contain an infusate volume of from 1 to 20 milliliters, and to deliver this volume over a period of from two hours to seven days. The specific volume of infusate contained and total delivery time would vary depending on the choice of infusate, and would not necessarily be restricted to these quantities.

#### CLAIMS

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We claim:

1. A portable infusion device assembly comprising:
  - a. a first pouch containing infusate and a dispensing nozzle,
  - b. a second pouch containing a driving medium in pressure transmitting relationship to the aforesaid first pouch,
  - c. an integral power source comprising:
    - a pressure generating means for generating pressure in aforesaid driving medium,
    - an activating means for initiating the action of the aforesaid power generating means,
  - d. a rate-controlling means for regulating the volume change of the aforesaid first pouch,
  - d. a connecting means for attaching the aforesaid dispensing nozzle to the object of treatment and,

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e. a housing comprised of shape retaining walls containing the aforesaid first pouch, second pouch and power source and in restraining relationship with the aforesaid first and second pouches.

2. A portable infusion device assembly comprising:

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a. a first pouch containing infusate and a dispensing nozzle,

b. a second pouch containing a driving medium in pressure transmitting relationship to the aforesaid first pouch,

c. an integral power source comprising:

a pressure generating means for generating pressure in aforesaid driving medium,

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an activating means for initiating the action of the aforesaid power generating means,

a rate controlling means for regulating the volume change of the aforesaid first pouch,

15

d. a connecting means for attaching the aforesaid dispensing nozzle to the object of treatment and,

e. a housing comprised of shape retaining walls containing the aforesaid first pouch, second pouch and power source and in restraining relationship with the aforesaid first and second pouches.

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3. The device according to claim 1 where:

a. the pressure generating means is comprised of:

a gas generating electrolytic cell,

b. the rate controlling means is a electrical circuit operated in such a manner as to control the rate of gas formation and,

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c. the driving medium is gaseous.

4. The device according to claim 1 where:

a. the pressure generating means is comprised of:

a gas under pressure,

- b. the rate controlling means is a valve operated in such a manner as to control the rate of gas flow and,
- c. the driving medium is gaseous.

5. The device according to claim 1 where:

- a. the pressure generating means is comprised of:  
a mechanical means for increasing the pressure of the pressure-transmitting pouch,
- b. the rate controlling means is obtained by operating the aforesaid mechanical means in such a manner so as to control the rate of pressure formation and,
- c. the driving medium is liquid.

10. The device according to claim 1 where:

- a. the pressure generating means is comprised of:  
a mechanical means for increasing the pressure of the pressure-transmitting pouch,
- b. the rate controlling means is obtained by operating the aforesaid mechanical means in such a manner so as to control the rate of pressure formation and,
- c. the driving medium is gaseous.

15. The device according to claim 1 where the inner space of first infusate pouch is comprised of:

- a. drug in dry form,
- b. pharmaceutically acceptable solvent for said drug and,
- c. a breakable seal in separating relationship to said drug and solvent.

20. The device according to claim 2 where:

- a. the pressure generating means is comprised of:  
a gas generating electrolytic cell,
- b. the rate controlling means is a electrical circuit operated in such a

manner as to control the rate of gas formation and,

- c. the driving medium is gaseous.

9. The device according to claim 2 where:

- a. the pressure generating means is comprised of:  
5 a gas under pressure,  
b. the rate controlling means is a valve operated in such a manner as to control the rate of gas flow and,  
c. the driving medium is gaseous.

10. The device according to claim 2 where:

- a. the pressure generating means is comprised of:  
10 a mechanical means for increasing the pressure of the pressure-transmitting pouch,  
b. the rate controlling means is obtained by operating the aforesaid mechanical means in such a manner so as to control the rate of pressure formation and,  
15 c. the driving medium is liquid.

11. The device according to claim 2 where:

- a. the pressure generating means is comprised of:  
20 a mechanical means for increasing the pressure of the pressure-transmitting pouch,  
b. the rate controlling means is obtained by operating the aforesaid mechanical means in such a manner so as to control the rate of pressure formation and,  
c. the driving medium is gaseous.

25 12. The device according to claim 1 where the inner space of first infusate pouch is comprised of:

- a. drug in dry form,  
b. pharmaceutically acceptable solvent for said drug and,

c. a breakable seal in separating relationship to said drug and solvent.

13. A method for infusing a patient, comprising connection of said patient to a portable infusion device, said device comprising:

5 a. a first pouch containing infusate and a dispensing nozzle,

b. a second pouch containing a driving medium in pressure transmitting relationship to the aforesaid first pouch,

c. an integral power source comprising:

a pressure generating means for generating pressure in aforesaid driving medium,

10 an activating means for initiating the action of the aforesaid power generating means,

a rate controlling means for regulating the volume change of the aforesaid first pouch,

d. a connecting means for attaching the aforesaid dispensing nozzle to the object of treatment,

15 e. a housing comprised of shape retaining walls containing the aforesaid first pouch, second pouch and in restraining relationship with the aforesaid first and second pouches.

f. activating said device.

20 14. A method for infusing a patient, comprising connection of said patient to a portable infusion device, said device comprising:

a. a first pouch containing infusate and a dispensing nozzle.,

b. a second pouch containing a driving medium in pressure transmitting relationship to the aforesaid first pouch,

25 c. an integral power source comprising:

a pressure generating means for generating pressure in aforesaid driving medium,

an activating means for initiating the action of the aforesaid power

generating means,

a rate controlling means for regulating the volume change of the aforesaid first pouch,

- d. a connecting means for attaching the aforesaid dispensing nozzle to the object of treatment and,
- e. a housing comprised of shape retaining walls containing the aforesaid first pouch, second pouch and power source and in restraining relationship with the aforesaid first and second pouches.
- f. activating said device.

- 10 15. The device according to claim 1 where the drug contained in the infusate pouch is heparin.
- 16. The device according to claim 1 where the drug contained in the infusate pouch is insulin.
- 17. The device according to claim 2 where the drug contained in the infusate pouch is heparin.
- 15 18. The device according to claim 2 where the drug contained in the infusate pouch is insulin.

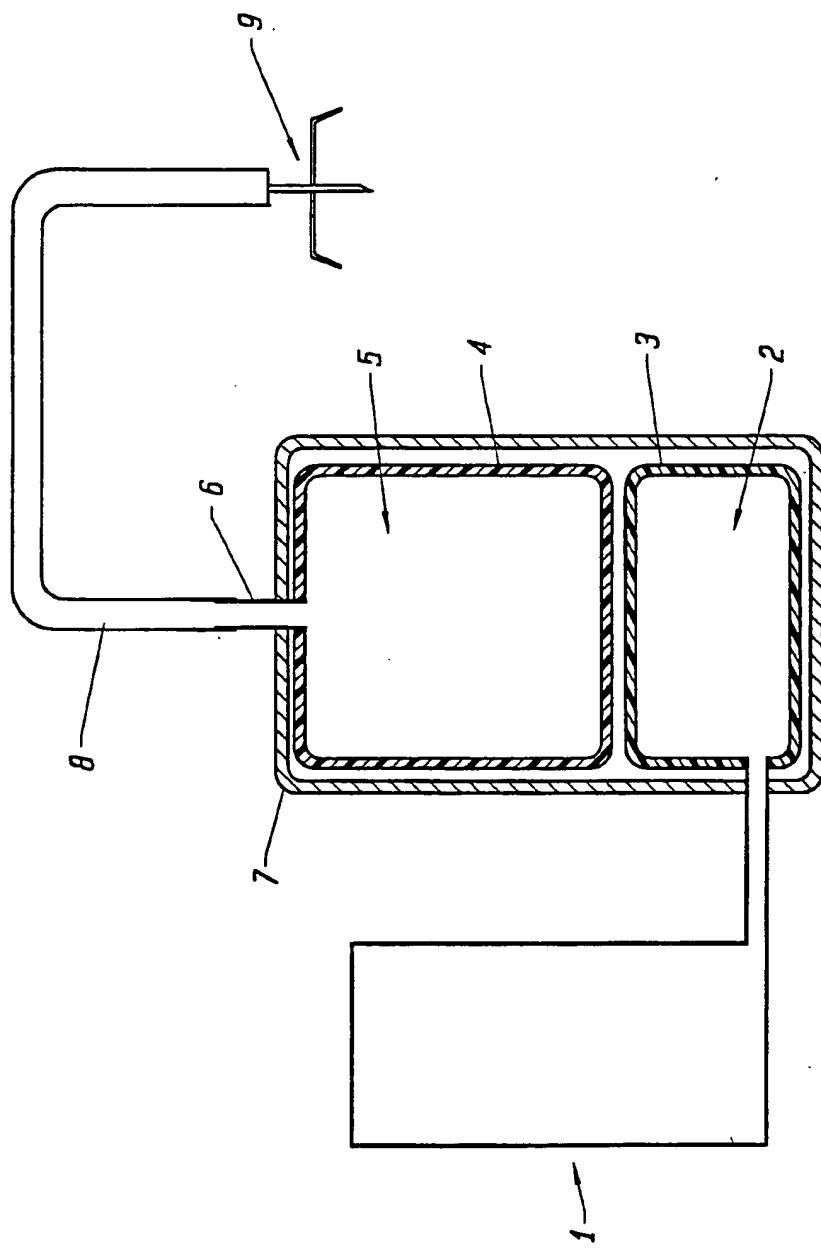


FIG. 1

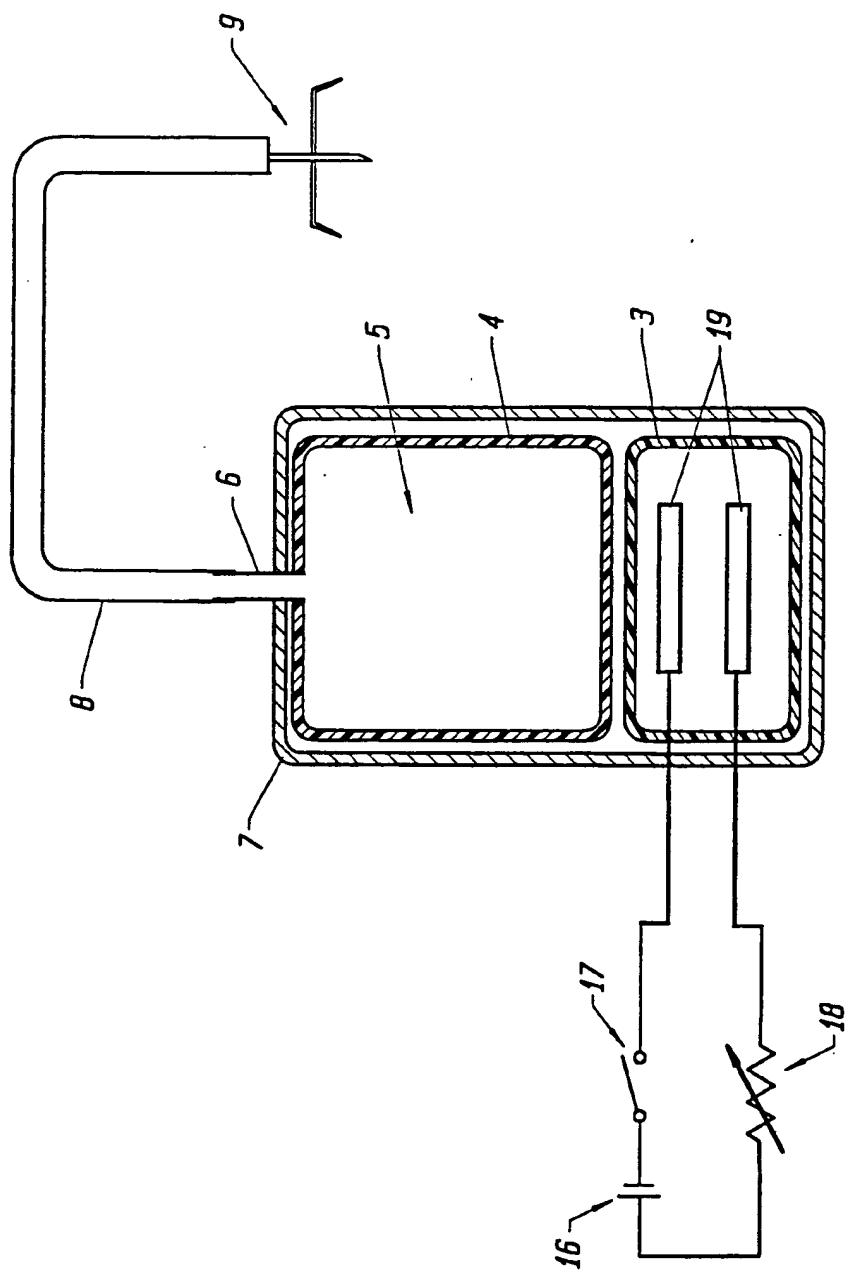


FIG. 2

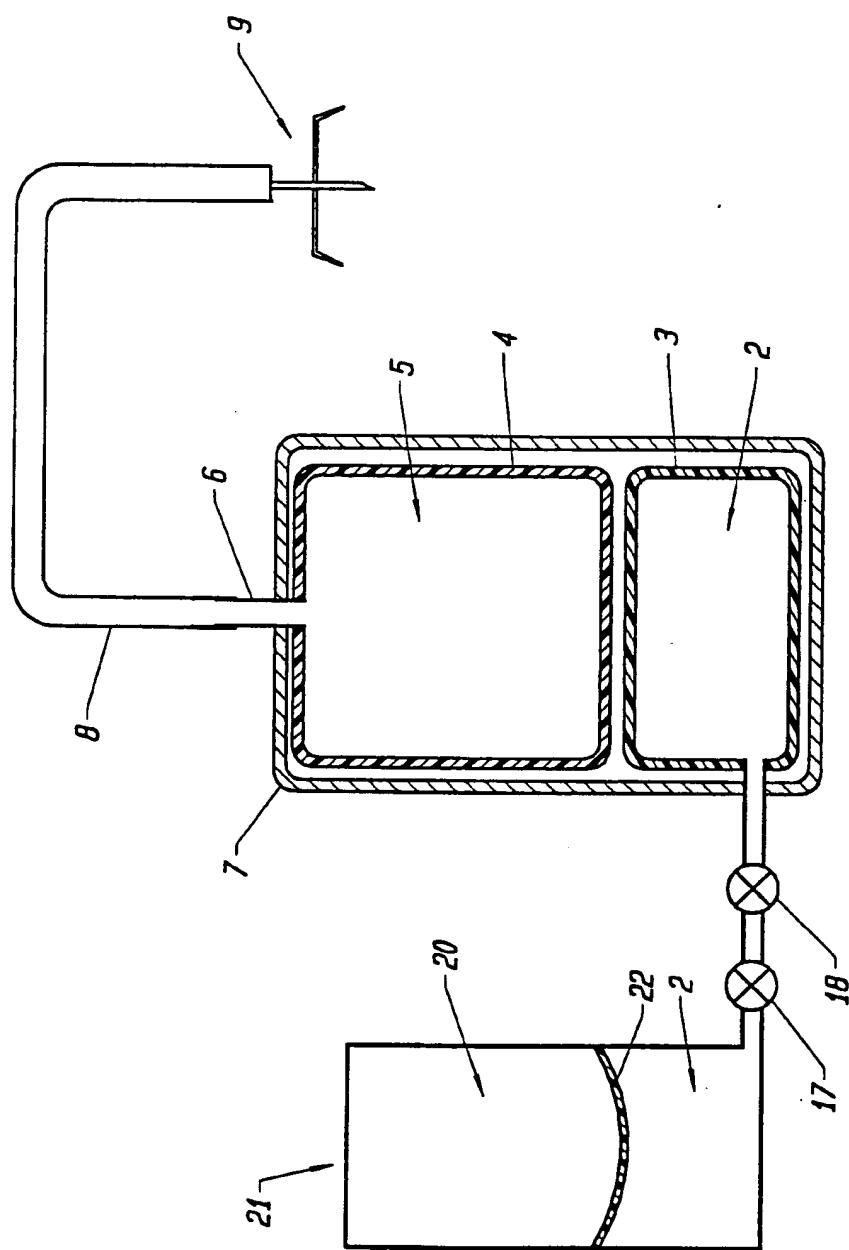


FIG. 3

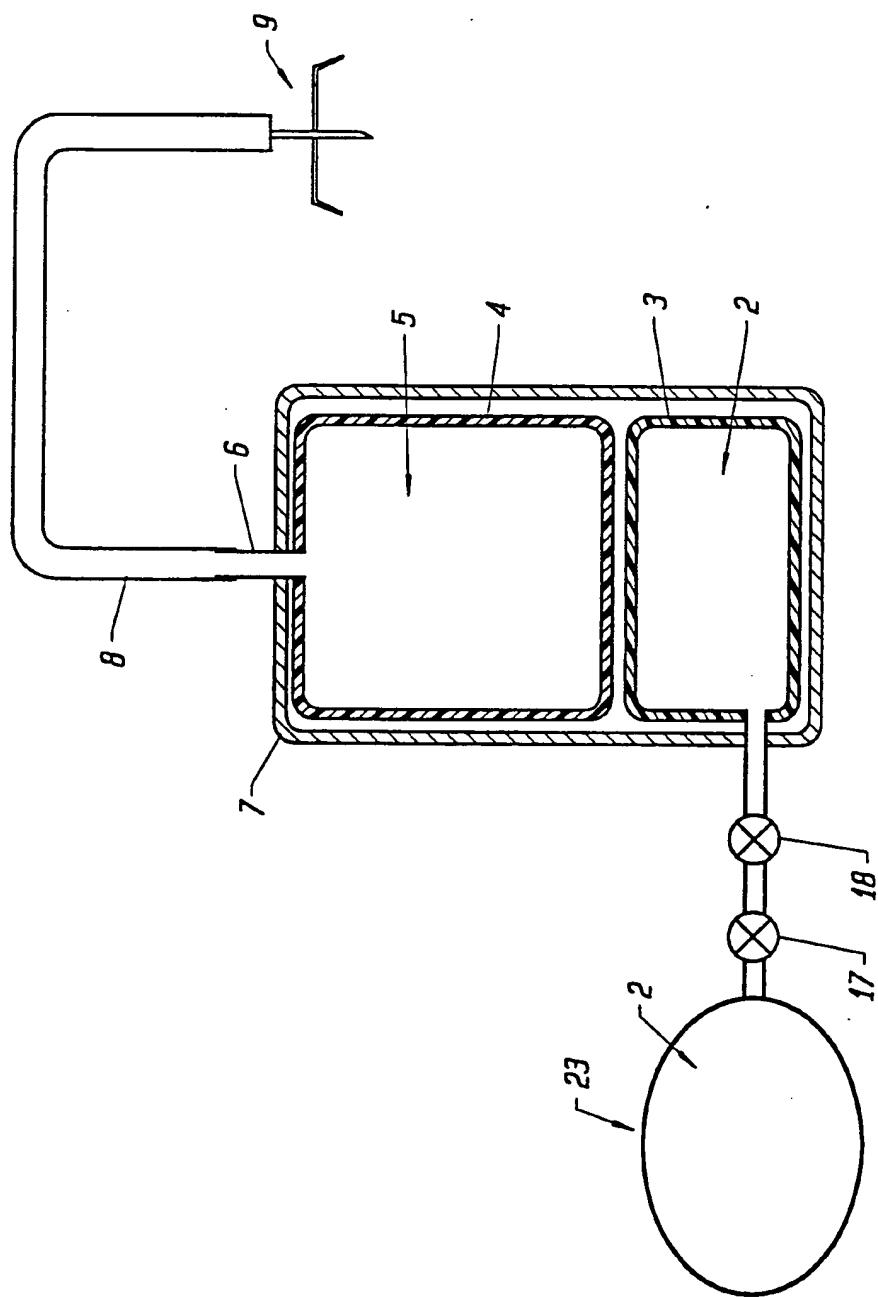


FIG. 4

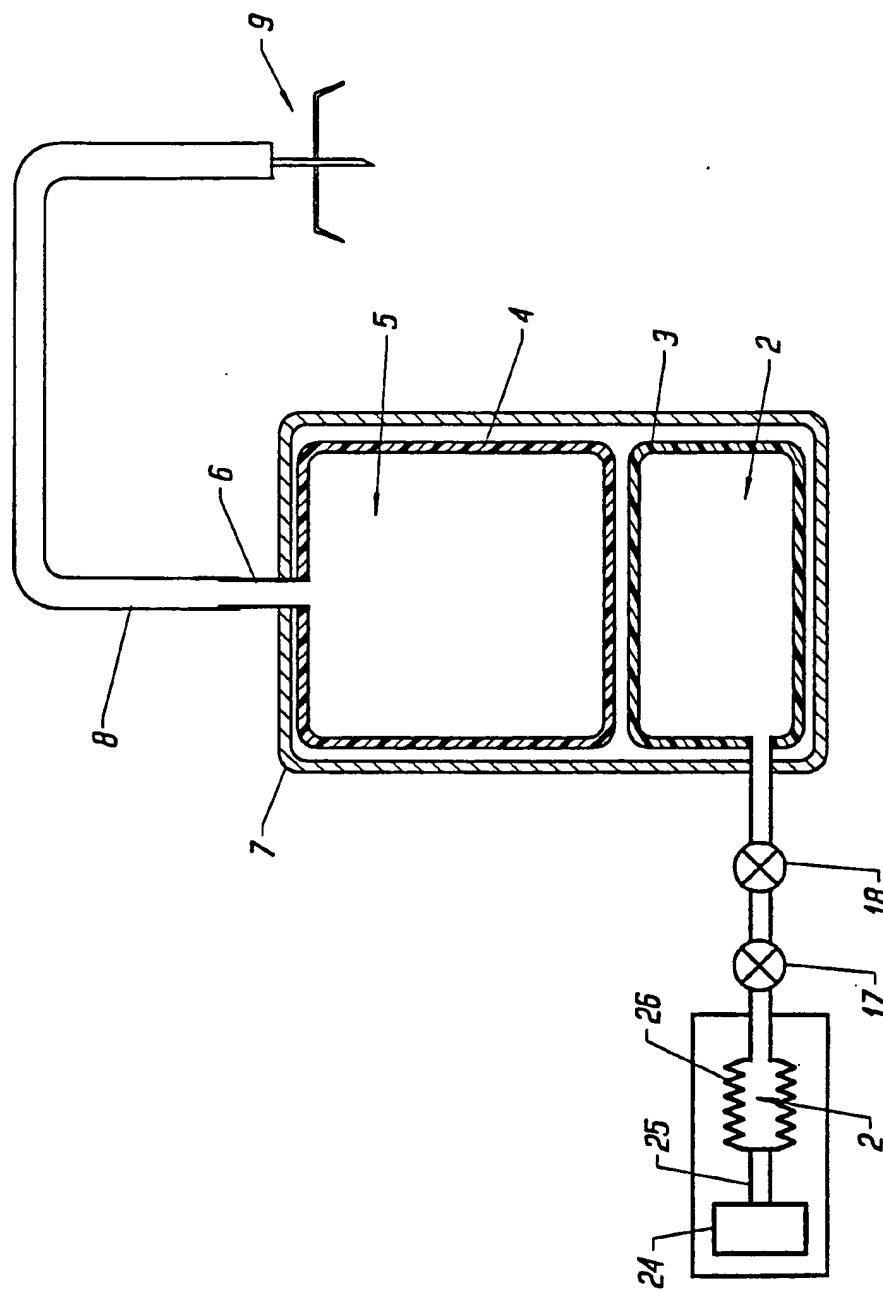


FIG. 5

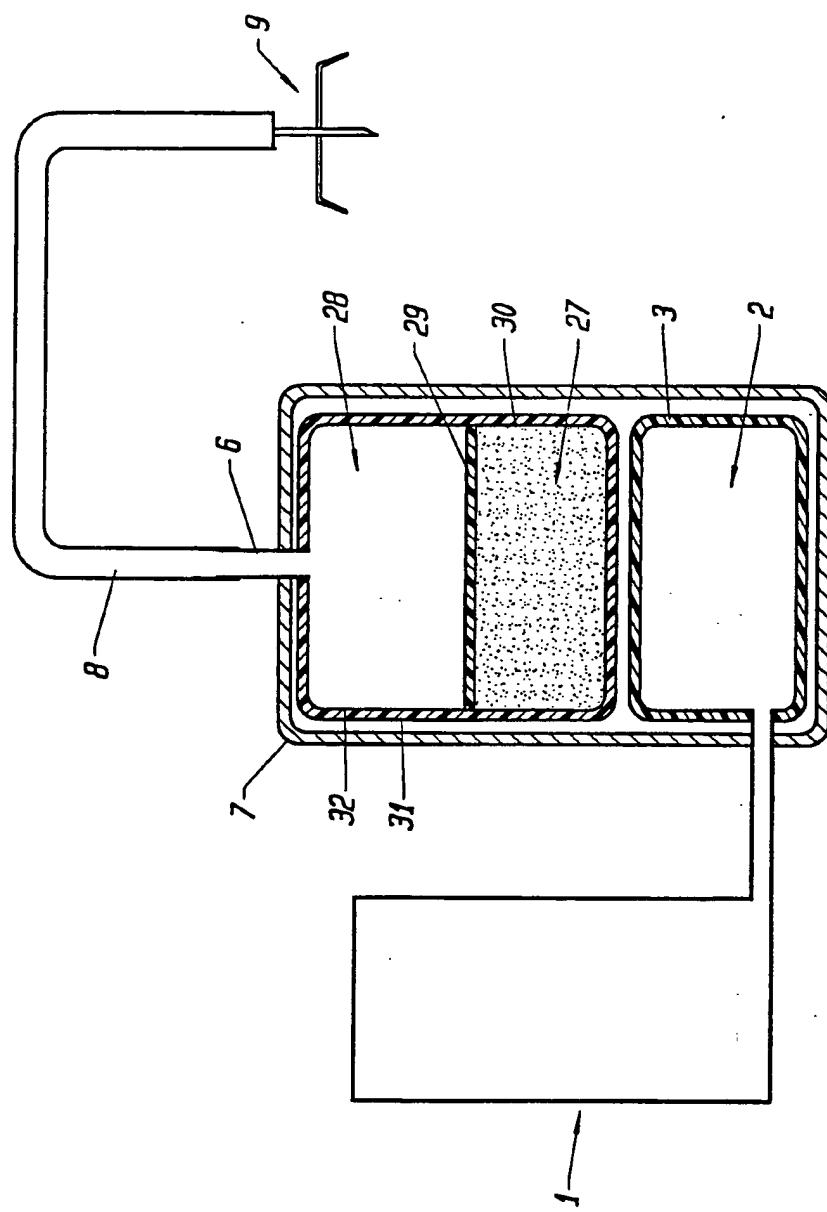


FIG. 6

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11660

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 37/00

US CL :604/141, 153, 410

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/87, 131, 140, 141, 145-147, 153, 410, 416

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	US, A, 3,895,741, (NUGENT), 22 July 1975. See whole document.	1, 2, 4, 6, 9-11 13-18
Y	US, A, 4,640,445, (YAMADA), 03 February 1987. See whole document.	3, 8
Y	US, A, 3,023,750, (H. C. BARON), 06 March 1962. See whole document.	1, 2, 4, 6, 9-11, 13-18
Y	US, A, 4,608,043, (LARKIN), 26 August 1986. See whole document.	7, 12
Y	US, A, 4,886,514, (MAGET), 12 December 1989. See whole document.	1, 18
A	US, A, 4,432,763, (MANSCHOT ET AL.), 21 February 1984. See whole document.	1-18

 Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	X	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Y	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

21 JUNE 1994

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International application No. PCT/US93/11660
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,458,733, (LYONS ET AL.), 10 July 1984. See whole document.	7, 12
A	US, A, 4,684,367, (SCHAFFER ET AL.), 04 August 1987. See whole document.	1-18
Y	US, A, 5,062,834, (GROSS ET AL.), 05 November 1991. See whole document.	3, 8
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